In the Claims:

Claim 1. (Four times amended) An adjuvant composition comprising:

(1) a metabolizable oil and

(2) an emulsifying agent, wherein said oil and said emulsifying agent are present in the form of an oil-in-water emulsion having oil droplets substantially all of which are less than 1 micron in diameter and wherein said composition [does not require muramyl peptides and] exists in the absence of any polyoxypropylene-polyoxyethylene block copolymer and in the absence of any muramyl peptide.

REMARKS

The Present Invention:

The present invention relates to vaccine adjuvant compositions. The discovery at the core of this invention was that certain oil-in-water emulsions having oil droplets substantially all of which are less than 1 micron in diameter exhibit unexpectedly high adjuvant activity. This high activity means that these adjuvants can be used as the active adjuvant component of antigenic compositions for the treatment and/or

prophylaxis of infection with pathogens. These adjuvant compositions represent a significant advance over the only adjuvant currently approved for human use ("alum", i.e., aluminum salts).

As used herein, an adjuvant means a substance that increases the immune response to an antigen when administered with the antigen.

Office Action:

Claims 1-9, 29, and 36 are currently pending in the application. These claims stand rejected under 35 U.S.C. § 112, first and second paragraphs 35 U.S.C. § 102(b) as allegedly being anticipated by Mizushima et al., U.S. 4,613,505; and Mizushima, further in view of Glass et al., U.S. 3,919,411. 35 U.S.C. § 103 as allegedly being obvious over either (i) Hoskinson, et al., U.S. 5,109,026 in view of Mizushima or (ii) Hoskinson and

Each of these rejections is addressed in turn below and, as explained, Applicants submit that none of these rejections should be maintained and that the claims are in condition for allowance.

Rejections Under 35 U.S.C. § 112, First Paragraph

Two general rejections are given under this statutory section, and these are numbered as (1) and (2) in the following discussion (responding to paragraphs 3-7 of the present Office Action).

(1) In the Office Action, it is alleged that the present specification and pending claims do not enable an adjuvant composition in the absence of a muramyl peptide. (As an aside, it should be noted that Claim 1 has been amended, pursuant to paragraph 8 of the Office Action, to recite that the claimed compositions lack a muramyl peptide, rather than just that muramyl peptides are not required; see discussion below.) Applicants disagree with this allegation for the following reasons.

First, as described above, the present invention relates to the discovery that submicron oil-in-water emulsions can themselves function as adjuvants without the necessity of additional immunostimulatory agents. As used herein, an adjuvant refers to a substance that increases the immune response to an antigen when administered with the antigen (see also Hoskinson et al., U.S. 5,109,026, column 1, lines 24-28). While the Examiner

is correct in noting that the specific Examples only refer to submicron oil-in-water emulsions either prepared with a muramyl peptide or to which a muramyl peptide was later added (see, e.g., page 58, lines 9-30), the specification itself teaches one of ordinary skill to practice the invention with or without a muramyl peptide.

The presence or absence of muramyl peptides, however, is not a critical feature of the present invention. This is discussed, for example, on page 3, lines 33-38, continuing onto page 4, lines 1-9, wherein it is stated that these submicron oil-in-water emulsions themselves provide satisfactory adjuvant formations. It is noted that these compositions can also contain an immunostimulating agent, which can either be the same as the emulsifying agent--as is the case with muramyl peptides. Another such discussion appears on page 17, lines 17-38, continuing onto page 18, lines 1-11, wherein it is noted that, "The emulsifying agent need not have any specific immunostimulating activity, since the oil composition by itself can function as adjuvant when the oil droplets are in the submicron range." (page 17, lines 20-23). (Additionally, originally filed claims 1 and 10 also show this distinction, as does the Abstract, page 67.)

Furthermore, scientific publications by the assignee of the present invention or by recipients of assignee's formulations clearly demonstrate that a muramyl peptide is not necessary and that, following the teaching of the specification, one could prepare adjuvant compositions either with or without muramyl peptides. See, e.g., Ott et al., MF59: Design and Evaluation of a Safe and Potent Adjuvant for Human Vaccines, in Vaccine Design: The Subunit and Adjuvant Approach, edited by M.F. Powell et al., Plenum Press, New York (1995) (page 283, Table II wherein superscript b refers to adjuvant compositions having MTP-PE and superscript c refers to adjuvant compositions lacking MTP-PE. As can be seen, all formulations generate higher antibody titers than vaccines formulated with alum); Ott et al., Vaccine 13:1557-1562 (1995) (Abstract, lines 9-11; Table 4, MF59-0 (lacking a muramyl peptide, MTP-PE) compared with MF59-100 (having MTP-PE), and text on page 1560, second column, lines 29-38); Higgins, et al., Vaccine 14:478-484 (1996) (description of adjuvant without MTP-PE on page 479); Zhu et al., Scand J. Immunol. 42:557-563 (1995) (description of adjuvant without MTP-PE on page 558); Langenberg et al., Ann. Intern. Med. 122:889-898 (1995) (page 889, Objective and Results) (copies of these articles are

provided for the convenience of the Examiner). Thus, in a variety of animals, both nonhuman and human, and for a variety of disease targets, the data demonstrate that, as taught in the specification, Applicants' adjuvant compositions do not require a muramyl peptide.

It is respectfully submitted that the current rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

(2) The present Office Action maintains that the specification and claims do not enable a person of ordinary skill in the art to practice the claimed invention without undue experimentation. Applicants disagree with this statement.

In every species of animal tested (including humans) with a variety of disease targets, Applicants' adjuvant compositions generated higher (3- to 50-fold) antibody titers (as measured by ELISA or viral neutralization assays) when compared with the only currently approved vaccine adjuvant (alum). Referring to Table I of Ott et al., in Vaccine Design (cited above), the present adjuvants were used in vaccines against herpes simplex virus (HSV), human immunodeficiency virus (HIV), influenza (flu), hepatitis C virus (HCV), cytomegalovirus (CMV), hepatitis B virus (HBV), human papilloma virus (HPV), and malaria. A variety of

animal species (infants, adults, and elderly animals) were used. As can be seen from Table I, there were no negative results (i.e., less than 3-fold higher antibody titers than those raised by alum).

This effect extends to human clinical trials, see Langenberg et al., page 896, discussing HSV antibody titers using Applicants' adjuvant that resulted in a 100-fold increase compared with those achieved with alum.

To date, over 6,000 human subjects in clinical trials have received Applicants' submicron oil-in-water vaccine adjuvants with five different vaccines (HIV, HSV, CMV, HBV, and flu) in infant, adult, and elderly age cohorts. In all cases, the use of these adjuvants has significantly enhanced the immune responses (both humoral and cell-mediated immunity) of human subjects. Given the variety and amount of preclinical and clinical experience that has arisen from Applicants' teachings, it is respectfully submitted that the current rejection based on alleged unpredictability should be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph:

It is believed that the amendment to Claim 1 removes this rejection. As noted above, muramyl peptides are not required in the present invention, although they are one of many preferred embodiments. (Claims requiring the presence an additional immunostimulating agent, including but not limited to muramyl peptides, are being prosecuting in co-pending USSN 08/434,677, filed May 4, 1995, as a divisional of the present application.)

Rejection Under 35 U.S.C. § 102(b):

Claims 1, 5, 6, and 9 stand rejected as allegedly anticipated by Mizushima, et al., US 4,613,505. The disclosure in Mizushima is not related in any way to vaccines or vaccine adjuvants. Rather, it relates to a fat emulsion of esters of flurbiprofen. Such esters have antiinflammatory, analgesic, and antipyretic activity. Such esters are formulated in emulsions that facilitate the activity of a known drug with certain functions. There is absolutely no teaching or suggestion that such emulsions should be used for any purpose apart from formulation with these active esters. Nor is there any teaching or suggestion that these emulsions alone would provide antiinflammatory, analgesic, and antipyretic activity.

Applicants' claims specify that the invention is a "adjuvant composition." As discussed above, the term "adjuvant" has a specific medical connotations, i.e., an adjuvant means a substance that increases the immune response when administered with an antigen. As such, Applicants' claims are novel over Mizushima. The disclosure of the latter does not include adjuvants, much less emulsions having activity apart from the active agent (in the case of Mizushima, flurbiprofen esters). Furthermore, the small size of Mizushima's fat emulsions is said to be advantageous for stability against heat sterilization and for long-time storage (column 3, lines 8-11). In contrast, the submicron size of Applicants' has significant adjuvant activity: the claimed compositions are vaccine adjuvants in their own right, and do not rely upon exogenous chemicals for its immunologically useful properties.

Therefore, by specifying in the claims that the present compositions are adjuvant compositions, Applicants' invention is novel over Mizushima, and it is respectfully requested that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103:

Applicants' invention is also alleged to be obvious over either (i) Hoskinson, et al., U.S. 5,109,026 in view of Mizushima or (ii) Hoskinson and Mizushima, further in view of Glass et al., U.S. 3,919,411.

As discussed above Mizushima does not teach or suggest submicron adjuvant compositions capable of enhancing an immune response. Rather, Mizushima relates to emulsions having small size for stability and storage, and lacking inherent activity.

The combination of Mizushima and Hoskinson et al., U.S. 5,109,026 is improper. The former reference relates to inactive emulsions for non-vaccine candidates, and the latter relates to vaccine adjuvants. Both of these fields are separate and distinct, and one of ordinary skill in the art would not make such a combination, absent an explicit suggestion to do so. Assuming, however, that such a combination is permissible, Applicants' invention is still not rendered obvious by the two references.

Hoskinson advocates the combination of polycationic polyelectrolyte immunoadjuvants and oil emulsions, useful for stimulating an immune response against an antigen. It should be

noted that Hoskinson teaches that water-in-oil emulsions are preferable over oil-in-water emulsions (see column 3, lines 22-24). Also, Hoskinson consistently refers to the tested oil emulsions as representative of the prior art (see, e.g., column 6, line 29), and teaches away from using such emulsions as adjuvants. It is the combination of oil emulsions with polycationic polyelectrolyte adjuvants that is taught to be superior, not the oil emulsions themselves. There is no teaching or suggestion to enhance the activity of oil emulsion adjuvants without the addition of a second specified adjuvant. On the other hand, Applicants' invention has shown significant advantages over oil emulsion adjuvants (such as Incomplete Freund's Adjuvant (IFA), which is unacceptable for human use) (see, e.g., Van Nest et al., Vaccines 92:57-62 (1992) (page 60, Figure 2a, copy enclosed for the convenience of the Examiner).

The further addition of Glass et al., U.S. 3,919,411, does not render Applicants' invention obvious. Glass describes the use of a macromolecular synthetic resin wherein the oil component must be about 25 percent by volume of the total system, with a maximum of 85 percent (column 5, lines 59-62). Applicants' adjuvant, by contrast, is limited to 0.5 to 20% total volume

(most preferred from 1-4%). The type of adjuvant described by Glass has very different properties from those of Applicants. Specifically, Glass's adjuvants act through depot action (i.e., material holding the antigen at the injection site so that the antigen is slowly released). This is basically a variation on IFA with the required addition of a synthetic resin matrix to bind the antigens for slow release (see Abstract, lines 10-16). (See Applicants' Amendment of December 22, 1994, in the parent application for a schematic representation of these different adjuvants.)

Applicants' adjuvant compositions do not serve as depots for antigen release. Instead, the antigen, as well as the adjuvant itself, is rapidly dispersed the site of introduction, resulting in direct immunostimulatory effects. In sum, there is no teaching or suggestion from Glass in combination with Hoskinson and Mizushima that would direct one to formulate low viscosity, submicron oil-in-water emulsion adjuvants having direct immunostimulatory effects. Applicants respectfully request that these rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the amendments and remarks contained herein, Applicants respectfully request that the current rejections be withdrawn and that Claims 1-9, 29, and 36 be allowed.

If the Examiner believes that a telephone interview would expedite prosecution of this application, the Examiner is invited to contact the undersigned at (510) 601-2708.

Respectfully submitted,

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